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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,797	08/05/2003	Jean Rapin	10945.105002 (Neuro 101US	2719

EXAMINER	
CORDERO GARCIA, MARCELA M	

ART UNIT	PAPER NUMBER
1654	

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DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/635,797	RAPIN ET AL.	
	Examiner	Art Unit	
	Marcela M Cordero Garcia	1654	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/03 and 04/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 and 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite because it is unclear as to whom or to what this effective amount is being administered. Therefore claim 1 currently reads on administering to any kind of subject, such as snails, bacteria, inanimate matter, etc. In addition, as drafted, claim 1 reads on administering to a subject in need thereof (therapeutic mode) and to a subject not in need thereof (prophylactic mode).

Claim 1 is rendered vague and indefinite by the phrase: "...R_1 is a residue from one of the aminoacids Phe, Tyr, Trp, Pro, which each may be optionally substituted with one or more (C_{1-5}) alkoxy groups, (C_{1-5}) alkyl groups or halogen atoms, as well as Ala, Val, Leu or Ile;". The claim is indefinite for the following reasons:

a) It is not clear what the meaning of "optional substitution" is, e.g., does it mean replacing a hydrogen atom in the aromatic or proline rings for a different group, or does it mean modifying the amino acid residue in a different way, for example, replacing a

hydrogen in the aliphatic portion of the residue or replacing an atom other than hydrogen?

b) It is not clear whether Ala, Val, Leu or Ile are to be optionally substituted within the amino acid residues Phe, Tyr, Trp and Pro, or if they are residues that can replace R_1 but that should not be optionally substituted.

Claim 11 is rendered vague and indefinite by the phrase: "A pharmaceutical composition comprising compounds of the following formula (I)..." because it is unclear how many compounds form the pharmaceutical composition, it is suggested that the claim be rephrased to "A pharmaceutical composition comprising one or more compounds of the following formula (I)...".

Claim 11 is rendered vague and indefinite by the phrase "R_1 is a residue derived from one of the amino acids Phe, which may be optionally substituted with one or more (C1-5) alkoxy groups, (C1-5) alkyl groups or halogen atoms;...". It is not clear whether "optionally substituted" means replacing a hydrogen atom in the aromatic or proline rings for a different group, or modifying the amino acid residue in a different way, for example, replacing a hydrogen in the aliphatic portion of the residue or replacing an atom other than hydrogen. In addition, the phrase "R_1 is a residue derived from one of the amino acids Phe" is unclear because it only recites one amino acid.

Claim 14 recites the limitation "N,N-diethyl-isoleucyl-isoleucyl-prolineamide" in claim 11. There is insufficient antecedent basis for these limitations in the claim, because in claim 11, R_1 is defined as phenylalanine (Phe), but not as isoleucine (Ile).

Claim 16 is rendered vague and indefinite by the phrase: "...R_1 is a residue which is derived from Phe which is optionally substituted with one or more (C_{1-5}) alkoxy groups, (C_{1-5}) alkyl groups or one or more halogen atoms" because it is not clear whether "optional substitution" means replacing a hydrogen atom in the aromatic ring for a different group, or modifying the amino acid residue in a different way, for example, replacing a hydrogen in the aliphatic portion of the residue or replacing an atom other than hydrogen.

Claim 17 recites the limitation "R_1 is a residue which is... derived from the amino acid Ile" in claim 11. There is insufficient antecedent basis for these limitations in the claim, because in claim 11, R_1 is defined as phenylalanine (Phe), but not as isoleucine (Ile).

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, second paragraph for the reasons set forth above.

With respect to the art rejections below, please note the following:

Alzheimer's disease, as referenced by Kan (Eur J Med Chem, 1992) is known in the art to be associated to brain lesions (amyloid β-protein plaques) whose composition is toxic (see, e.g., page 565, column 2 and page 566, column 1). Therefore, based upon the reference teachings, Alzheimer's disease can be classified as a postlesional disease of toxic origin.

In addition, please note that amnesia, as referenced by http://www.smithsrisca.demon.co.uk/neuro-glossary.html (accessed online, October 4, 2004), is known in the art to be associated, i.a., with bilateral lesions of either the hippocampal regions or the mammillary bodies, that may have originated by a mechanical or physical agent (trauma) (http://accessscience.com/, search term 'trauma', accessed online, October 4, 2004), and therefore can be classified as a postlesional disease of traumatic origin.

Alzheimer's disease and amnesia are known in the art to be neurodegenerative disorders, as referenced by Henrichwark et al. (US 6080848). Ischemic heart disease may be caused, as is known in the art and referenced by Tedeshi et al. (US 6645518), by atherosclerotic lesions. Therefore ischemic heart disease can be classified as a postlesional disease of ischemic origin.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-7 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Masuyama et al. (US 6,410,685).

The instant claims are drawn to a method for the treatment of neurodegenerative diseases, comprising administering an effective amount of a proline derivative of formula (I). Specific species for the method are, e.g., L-valyl-L-prolyl-L-proline and L-isoleucyl-L-prolyl-L-proline. Please note that the administered subject has not been defined and therefore the claims read upon the method with subjects not affected by any of the diseases.

Masuyama et al. teach the administration of valyl-L-prolyl-L-proline and L-isoleucyl-L-prolyl-L-proline to rats (examples 4-7).

Therefore, the reference is deemed to anticipate the instant claims above, as drafted.

Claims 1-8, 11-12 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshimasa et al. (JP 09169797)

Yoshimasa et al. teach biodegradable pharmaceutical compositions of a tripeptide encompassed by formula (I), e.g., Pro-Phe-Pro and Pro-Phe-Pro-NH_2 (see, e.g., abstract and example 3). These compositions inherently read upon a method of administration to a subject as it is indicated that the composition is decomposed in a living body and metabolized with no side effects (see, e.g., abstract).

Therefore, the reference is deemed to anticipate the instant claims above.

Claims 1-8, 11-12 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshimasa et al. (JP 09040577)

Yoshimasa et al. teach biodegradable pharmaceutical compositions of a tripeptide encompassed by formula (I), e.g., Pro-Phe-Pro and Pro-Phe-Pro-NH_2 (see, e.g. abstract and example 3). These compositions inherently read upon a method of administration to a subject as it is indicated that the composition is decomposed in vivo and metabolized with no side effects (see, e.g., abstract).

Therefore, the reference is deemed to anticipate the instant claims above.

Claims 1, 3-9, 11 and 16 are rejected under U.S.C. 102(b) as being anticipated by Hathaway et al. (WO 92/13549).

Hathaway et al. teach administration to rabbits of pharmaceutical compositions of peptides encompassed by formula (I), e.g., (see, e.g., abstract, pages 9-11 and 36-37).

Therefore, the reference is deemed to anticipate the instant claims above.

Claims 1, 3-8, 11 and 16 are rejected under U.S.C. 102(b) as being anticipated by Maruyama et al. (EP 0445606 A1).

Maruyama et al. teach administration to rats of pharmaceutical compositions of peptides encompassed by formula (I) for (see e.g. page 2, lines 48-54).

Therefore, the reference is deemed to anticipate the instant claims above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masuyama et al. (US 6,410,685).

Masuyama et al. teach the administration of valyl-L-prolyl-L-proline and L-isoleucyl-L-prolyl-L-proline to rats (examples 4-7).

Based upon the overall beneficial teachings provided by Masuyama et al. with respect to such peptide compositions, it would have been obvious at the time of the invention to adjust particular conventional working conditions therein (e.g., chemically modifying amino acid residues by alkylation or alkoxylation, replacing amino acid residues, as well as the actual administration of such compound to a subject in need thereof). This type of adjustment is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the reference, especially in the absence of evidence to the contrary.

Claims 1-14 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshimasa et al. (JP 09169797).

Yoshimasa et al. teach the in vivo use of a pharmaceutical solution of, e.g. peptide Pro-Phe-Pro, which is encompassed by formula (I) (see, e.g., abstract).

Based upon the overall beneficial teachings provided by Yoshimasa et al. with respect to such peptide compositions, it would have been obvious at the time of the invention to adjust particular conventional working conditions therein (e.g., chemically modifying amino acid residues by alkylation or alkoxylation, replacing amino acid residues, as well as the actual administration of such compound to a subject in need thereof). This type of adjustment is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the reference, especially in the absence of evidence to the contrary.

Claims 1-14 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshimasa et al. (JP 09040577).

Yoshimasa et al. teach the in vivo use of a pharmaceutical solution of, e.g. peptide Pro-Phe-Pro, which is encompassed by formula (I) (see, e.g., abstract). Based upon the beneficial teachings provided by Yoshimasa et al., it would have been obvious

at the time of the invention to have carried out the adjustment of particular conventional working conditions (e.g., chemically modifying amino acid residues by alkylation or alkoxylation, replacing amino acid residues, as well as the actual administration of such compound to a subject in need thereof) and this is therefore deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the reference, especially in the absence of evidence to the contrary.

Claims 1-14 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hathaway et al. (WO 92/13549)

Hathaway et al. teach administration to rabbits of pharmaceutical compositions of peptides encompassed by formula (I) for (see e.g. abstract, pages 9-11 and 36-37). Yoshimasa et al. teach the in vivo use of a pharmaceutical solution of, e.g. peptide Pro-Phe-Pro, which is encompassed by formula (I) (see, e.g., abstract).

Based upon the overall beneficial teachings provided by Hathaway et al., it would have been obvious at the time of the invention to adjust particular conventional working conditions therein (e.g., amidating the proline, chemically modifying amino acid residues by alkylation or alkoxylation, replacing amino acid residues, as well as the actual administration of such compound to a subject in need thereof). This type of adjustment is therefore deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the reference, especially in the absence of evidence to the contrary.

Claims 1-14 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maruyama et al. (EP 0445606 A1).

Maruyama et al. teach administration to rats of pharmaceutical compositions of peptides encompassed by formula (I) for (see e.g. page 2, lines 48-54. Yoshimasa et al. teach the in vivo use of a pharmaceutical solution of, e.g. peptide Pro-Phe-Pro, which is encompassed by formula (I) (see, e.g., abstract).

Based upon the overall beneficial teachings provided by Maruyama et al., it would have been obvious at the time of the invention to adjust particular conventional working conditions therein (e.g., amidating the proline, chemically modifying amino acid residues by alkylation or alkoxylation, replacing amino acid residues, as well as the actual administration of such compound to a subject in need thereof). This type of adjustment is therefore deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the reference, especially in the absence of evidence to the contrary.

With respect to the art rejections above, it is noted that at least some of the cited references do not teach that the reference compositions can be used in the manner instantly claimed. However, the intended use of the claimed composition does not

patentably distinguish the composition, per se, since such undisclosed use is inherent in the reference composition. In order to be limiting, the intended use must create a structural difference, thus the intended use is not limiting (see, e.g., MPEP 2112).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10 and 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 10/635,805.

The instantly claimed invention and the invention claimed in Application '805 are both drawn to a method of treating or preventing neurodegenerative diseases and/or postlesional diseases (such as Alzheimer's disease, in both cases) comprising administering an effective amount of a proline derivative of formula (I), e.g., Val-Pro-Pro or Ile-Pro-Pro. Further, the instantly claimed method encompasses and/or is encompassed by the claimed method of Application '805.

This is a provisional obviousness-type double patenting rejection.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 11/03 and 04/04 were filed after the mailing date of the application on 08/05/2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marcela M Cordero Garcia
Patent Examiner
Art Unit 1654

MMCG 10-2004

CHRISTOPHER R. TATE
PRIMARY EXAMINER